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Transformation of Eucaryotic Cells by Polycyclic Hydrocarbons Occurring in Cigarette Smoke: Discrimination between the Importance of Various Enzymes.

At present, these investigators are studying the role of the mammalian enzymes epoxide hydratase and dihydrodiol dehydrogenase in the inactivation of mutagenic metabolites produced from polycyclic hydrocarbons occurring in cigarette smoke using the bacterial test system of Ames. Addition of pure epoxide hydratase reduces the mutagenicity of benzo(a)pyrene when activated by liver microsomes from control mice, but increases the mutagenicity when microsomes from methylcholanthrene-treated mice are used for activation. Epoxide hydratase has no effect upon the activation of the 7,8- and the 9,10-dihydrodiols of benzo(a)pyrene. Preliminary results show that, in contrast, pure dihydrodiol dehydrogenase has no effect upon the mutagenicity of benzo(a)pyrene in the presence of control microsomes, but reduces the mutagenicity in the presence of microsomes from methylcholanthrene-treated mice. Control microsomes activate benzo(a)pyrene mainly to simple epoxides which can be inactivated by epoxide hydratase whilst microsomes from methylcholanthrene-treated animals activate benzo(a)pyrene mainly to dihydrodiol epoxides which are not inactivated by epoxide hydratase. However, the formation of these dihydrodiol epoxides can be reduced by dihydrodiol dehydrogenase. Thus both enzymes complement each other in inactivating mutagenic benzo(a)pyrene metabolites.

These encouraging results are leading the researchers to investigate the role of these enzymes by using the transformation of eucaryotic cells as an indication of carcinogenic activity. To perform these experiments they must (1) establish various in vitro cell transformation systems, (2) develop sensitive assays for the determination of the relevant enzyme activities (monooxygenase, epoxide hydratase, dioldehydrogenase and glutathione S-transferase) in the cultured cells, and (3) study the effect of addition of pure epoxide hydratase and dihydrodiol dehydrogenase to the cultures in the presence or absence of liver homogenate upon the cell transformation caused by polycyclic hydrocarbons.

In parallel, the investigators intend to study the interindividual variation in dihydrodiol dehydrogenase and epoxide hydratase activities in man using skin fibroblast and/or lymphocyte cultures. Activities will also be compared in cells from healthy individuals and from lung carcinoma patients.

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